REMARKS/ARGUMENTS

The invention claimed in the above-referenced application relates to a drug composition comprising sucrose and a lecithin-modified superoxide dismutase. As disclosed at page 16, lines 17-25, sucrose stabilizes the lecithin-modified superoxide dismutase (PC-SOD) against degradation due to cleavage (bond breaking) within the lecithin moieties. As a result of the stabilizing effect, the drug composition exhibits the characteristics listed at page 3, line 17 through page 4, line 16. These characteristics include: (a) complete dissolution of a lyophilized composition in water without precipitation of insoluble substances, (b) retention of at least 97% of the original activity of the material after lyophilizing and storage for 12 months at a temperature of 25°C or six months at a temperature of 40°C; (c) no observable difference in peak shape of PC-SOD before and after lyophilization and re-dissolution; and (d) no detectable difference in the amount of undesirable degradation products (analogues) measured before and after lyophilization and re-dissolution. Thus, the invention enhances properties and stability of PC-SOD by utilizing sucrose to prevent the cleavage (bond breaking) of the lecithin moieties of the PC-SOD molecule.

The Prior Art Rejection

There is only one issue remaining in the above-referenced application. That issue is whether the claims (1, 4, 6-8 and 10-14) are patentable under 35 U.S.C. §103(a) over JP 9-117279 in view of JP 1-304882.

The Examiner has taken the position that a person of ordinary skill in the relevant art seeking to store the SOD derivatives of JP '279 would recognize that the JP '882 reference teaches "that addition of sucrose would improve the storage stability of the SOD derivatives," and would have been motivated to combine "the SOD derivatives of the '279 reference with sucrose in order to render them stable for storage." The Examiner has further stated that one having ordinary skill in the art would have a reasonable expectation of success because JP '882 "discloses that the very same enzyme was rendered storage stable by combination with sucrose."

It is respectfully submitted that the proper standard under *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) has not been applied. In particular, obviousness is determined with respect to the knowledge of a person of ordinary skill in the pertinent art, not by a person without any substantial knowledge pertinent to the field of the invention. Further, the obviousness analysis has not taken into consideration the objective evidence of non-obviousness, as required under *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983). Finally, the rejection is based on the use of hindsight, which is impermissible under cases such as *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303, 313 (Fed. Cir. 1983), *cert. denied*, 469 US 851 (1984).

Those having ordinary skill in the art of preparing pharmaceutical compositions for the treatment of disease are typically very well educated and possess a comprehensive knowledge of organic chemistry and biochemistry. A person of ordinary skill in the pertinent art would typically have a Ph.D. in chemistry and/or pharmacology, would be fully cognizant of the technology described in the prior art, and would be capable of understanding the underlying chemistry. Thus, a person of ordinary skill in the art would understand that lecithin-modified superoxide dismutase (PC-SOD) is a chemical substance that is <u>different</u> from Cu and/or Zn-type SOD. PC-SOD is prepared by bonding lecithin to the human Cu/Zn-SOD. PC-SOD differs significantly from conventional SOD in distribution within a living body and affinity to self. Also, PC-SOD retains an extremely uniform activity, so that it is expected to enhance the pharmacological activity of SOD, reduce side-effects, and promote absorption (see JP 9-117279). By virtue of these differences, U.S. Patent No. 5,109,118 has been granted for claims to PC-SOD. Thus, human Cu/Zn-SOD differs very substantially from PC-SOD in chemical property and usage.

Because it is well known that PC-SOD behaves very differently from Cu/Zn-SOD, those having ordinary skill in the art would not expect sucrose to have the same stabilizing effect on PC-SOD as it does on Cu/Zn-SOD. In fact, it does not. The effect described in JP 1-304882 involves stabilizing human Cu/Zn-SOD solution in a frozen state or a lyophilized state (a single objective), whereas the claimed invention achieves <u>two</u> objectives: (1) inhibiting a reduction of the PC-SOD activity (maintaining stability) of a lyophilized PC-SOD material;

and (2) inhibiting degradation of PC-SOD by way of chemical bond cleavage within the lecithin moiety of lyophilized PC-SOD (as characterized by chromatographic techniques).

The fact that substances different in structure and properties can be stabilized by sucrose, does not render the invention obvious. The stabilizing effect of Applicants' invention is entirely different from that of the prior art. When human SOD is destabilized, it forms a dimer of human SOD. In contrast, when PC-SOD is destabilized, the lecithin moieties of the PC-SOD are cleaved at various sites to form analogues (various degradation products). Therefore, the degradation products are quite different. In other words, human SOD and PC-SOD are destabilized to produce different products. Destabilization of human SOD and PC-SOD take place at different reaction sites by different mechanisms. Accordingly, a person having ordinary skill in the art (i.e., a person capable of understanding the different chemical mechanisms responsible for degradation of human SOD and PC-SOD) would not expect an agent such as sucrose, which acts to inhibit degradation of human SOD by a first mechanism, to also inhibit degradation of a different molecule (PC-SOD) having different chemical properties and a different mechanism by which degradation occurs. It is only a person having considerably less than ordinary skill in the art and/or employing the benefit of hindsight, that could unreasonably expect that a compound (i.e., sucrose) that is effective for stabilizing a first compound (Cu/Zn-SOD) against a first type of degradation (i.e., dimerization) would also be effective at stabilizing a chemically different compound (PC-SOD) against a different type of degradation mechanism (degradation of lecithin moieties which are not even present in Cu/Zn-SOD).

Since the degradation mechanism of human SOD has no bearing on lecithin-modified SOD, and because the mechanism of PC-SOD degradation has no bearing on human SOD degradation, those having ordinary skill in the art would not expect a compound that stabilizes PC-SOD to also stabilize Cu/Zn-SOD, nor would one having ordinary skill in the art expect an agent that is effective for stabilizing Cu/Zn-SOD against degradation due to dimerization to also stabilize lecithin-modified SOD against degradation due to decomposition of lecithin moieties. For those having ordinary skill in the art at the time the invention was made, the ability of sucrose to stabilize both Cu/Zn-SOD and PC-SOD would have been unexpected,

since there was not any rationale for explaining why sucrose would inhibit two different types of degradation mechanisms on two different types of chemical molecules. The unexpected nature of the invention is further demonstrated by the fact that only sucrose has been found to be effective for stabilizing PC-SOD against degradation, whereas JP 1-304882 teaches that various other disaccharides, monosaccharides, and sugar alcohols are effective for stabilizing Cu/Zn-SOD against degradation. This is demonstrated in Applicants' examples which show that alanine, inositol, mannitol, sorbitol, creatinine, glycine, PEG 4000 and urea do not effectively stabilize PC-SOD. It is respectfully submitted that any proposed explanation as to why one having ordinary skill in the art would have expected sucrose to be effective in stabilizing lecithin-modified SOD against degradation due to decomposition of the lecithin moieties based on the disclosed ability of disaccharides, monosaccharides and sugar alcohols to stabilize Cu/Zn-SOD against a different type of degradation, should also explain the basis upon which those having ordinary skill in the art would be able to predict that alanine, inositol mannitol, sorbitol, creatinine, glycine, PEG 4000 and urea would not be effective for stabilizing PC-SOD. It is respectfully submitted that such explanation cannot be derived from the prior art. In fact, the inability of most disaccharides, monosaccharides and sugar alcohols to effectively stabilize PC-SOD would have been expected by those having ordinary skill in the art, and would have caused those having ordinary skill in the art to expect that sucrose would also be ineffective for stabilizing PC-SOD.

It is respectfully submitted that the rejection is not supported by the prior art, but is instead based on unscientific rationale and hindsight. This is demonstrated by the Examiner's statement that "a reasonable expectation of success would have been based on the fact that JP '882 disclosed that the very same enzyme was rendered storage stable by combination with sucrose." Aside from the fact that Cu/Zn-SOD and PC-SOD are different, not the same, and undergo degradation by different mechanisms, and therefore require different stabilization means, a further problem is that such expectation would not be met by any of the stabilizing agents disclosed in the JP '882 document, except for sucrose. It is surprising that sucrose is effective, not that the other disaccharides, monosaccharides and sugar alcohols are ineffective.

The Examiner has argued that Cu/Zn-SOD would be expected to behave exactly the same as PC-SOD, when the converse is known to be true. Extrapolating on the Examiner's argument, one could conclude that a compound which stabilizes a first compound against degradation due to dimerization would be expected to stabilize different compounds against different degradation mechanisms. The essence of this argument is that all stabilizers would be expected to stabilize all compounds against all degradation mechanisms, regardless of chemistry. It is submitted that this type of reasoning is inconsistent with the thinking of those having ordinary skill in the art. Specifically, those having ordinary skill in the art would not disregard the differences between the chemical mechanisms involved in stabilizing different compounds when developing an expectation.

CONCLUSION

In view of the above amendments and remarks, it is respectfully submitted that those having ordinary skill in the art would not expect sucrose to be an effective stabilizer against degradation of lecithin-modified superoxide dismutase based merely on the ability of sucrose to stabilize Cu-SOD and Zn-SOD against degradation due to dimerization. Therefore, it is submitted that the application is in condition for allowance and notice of same is earnestly solicited.

Respectfully submitted,

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